(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 210 540 B1**

# (12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification: 23.10.91 (51) Int. Cl.5: A61K 9/52, A61K 9/36

(21) Application number: 86109733.5

(22) Date of filing: 16.07.86

The file contains technical information submitted after the application was filed and not included in this specification

## (54) Time-controlled explosion systems and processes for preparing the same.

(30) Priority: 19.07.85 GB 8518301

(43) Date of publication of application:
04.02.87 Bulletin 87/06

(45) Publication of the grant of the patent:
23.10.91 Bulletin 91/43

(84) Designated Contracting States:
AT BE CH DE FR GB IT LI LU NL SE

(56) References cited:
EP-A- 0 077 956
DE-A- 1 617 724
FR-A- 848 389

(73) Proprietor: FUJISAWA PHARMACEUTICAL CO., LTD.
3, Doshomachi 4-chome Higashi-ku
Osaka-shi Osaka 541(JP)

(72) Inventor: Ueda, Yoshio
No. 1-3-5-204, Mikagenaka-machi
Higashinada-ku
Kobe-shi Hyogo(JP)
Inventor: Hata, Takehisa
No. 13-7, Nishikakiuchi Terado-cho
Muko-shi Kyoto(JP)
Inventor: Yamaguchi, Hisami
No. 17-12-705, Mondoso
Nishinomiya-shi Hyogo(JP)
Inventor: Ueda, Satoshi
No. 246-16, Nitta
Kawanishi-shi Hyogo(JP)
Inventor: Kodani, Masateru
No. 2-2-10, Midorigaoka
Ikeda-shi Osaka(JP)

(74) Representative: Türk, Gille, Hrabal
Brucknerstrasse 20
W-4000 Düsseldorf 13(DE)



EP 0 210 540 B1

## Description

This inv ntion relates to the Tim -Controlled Explosion Systems and to processes for preparing the same.

For further particulars, this invention relates to the Time-Controlled Explosion Systems which have sectional structures shown in Fig. 1, 2, 3 and 4, wherein (1) is a seed of sucrose (core), (2) is a drug, (2a) is a core comprising drug, (2b) is a mixture comprising drug and swelling agent, (3) is a swelling agent, and (4) is membrane, respectively. In these systems, the drug begins to release by the explosion of the outer membrane after a definite time period (defined as "lag times") when it is placed into the gastro-intestinal tract. By mixing the systems which have different lag times, the oral sustained release preparations with a various release patterns such as repeat pattern (i.e. drug release occurs repeatedly at every definite time), zero-order pattern (i.e. drug release is at uniform rate), reverse first-order pattern (i.e. drug release rate increases according to the passage of time), sigmoid pattern (i.e. drug release rate is slow at the initial and last stages and is fast at the middle stage) and so on can be obtained. Sustained release preparations can be used to reduce frequency of dosing, to prevent undesirable side effects and to get optimum therapeutic efficiency.

There are many approaches to prepare-the sustained release preparations. For example, there are preparations wherein drugs are compressed with a water-insoluble materials such as waxes and plastics into a tablet form or drug-coated beads or granules are coated with the various water-insoluble coating materials. However, these preparations have disadvantages that the release rate of the drug decreases according to the passage of time, and is influenced by pH of the gastro-intestinal fluid in case that the solubility of the drug is dependent on pH, and furthermore complete drug release from these preparations dose not occur.

An alternative approach is to prepare the sustained release preparation by mixing the granules of the non-sustained granules with the enteric-coated granules which dissolve in the intestine. As to this type of the preparations, there is possibility that the expected efficiency can not be obtained because the release of the drug is often influenced by the conditions of the gastro-intestinal tract such as pH and the emptying rate.

DE-A-1 617 724 discloses a composition comprising a mixture of a drug and a colloidal substance, for example gelatine, as a core and a outer membrane, for example ethylcellulose.

EP-A-0 077 956 relates to an enteric microcapsule comprising core material which is made of drug and swellable polymer material, and a coating wall which consists of ethylcellulose and an enteric polymer material.

We have carried out various studies in order to overcome the above-mentioned problems and invented a new type of the oral sustained release dosage form, namely, Time -Controlled Explosion Systems ( hereinafter referred to as T.C. E.S.). From the T.C.E.S., the drug is released by a quite novel mechanism which is neither diffusion control nor dissolution control.

Accordingly, the present invention is directed to a Time-Controlled Explosion System in which drug release is caused by explosion of outer membrane of a water-insoluble coating material after a definite time period, said System comprising a preparation in the form of a bead or granule, said preparation comprising a core which is covered with an outer layer of drug, a further layer of disintegrating agent selected from cellulose substituted with hydroxypropyl in which the ratio of hydroxypropoxyl groups is 5 to 16 weight percent , sodium starch glycolate and carboxymethylcellulose sodium, and an outer membrane of a water-insoluble coating material.

The present invention is furthermore directed to a Time-Controlled Explosion System in which drug release is caused by explosion of outer membrane of a water-insoluble coating material after a definite time period, said System comprising a preparation in the form of a bead or granule, said preparation comprising a core of a drug which is covered with an outer layer of disintegrating agent selected from cellulose substituted with hydroxypropyl in which the ratio of hydroxypropoxyl groups is 5 to 16 weight percent , sodium starch glycolate and carboxymethylcellulose sodium, and an outer membrane of a water-insoluble coating material.

A further embodiment of the present invention is a Time-Controlled Explosion System in which drug release is caused by explosion of outer membrane of a water-insoluble coating material after a definite time period, said System comprising a preparation in the form of a bead or granule, said preparation comprising a core which is covered with an outer layer of a mixture of a drug and a disintegrating agent selected from cellulose substituted with hydroxypropyl in which the ratio of hydroxypropoxyl groups is 5 to 16 weight percent , sodium starch glycolate and carboxymethylcellulose sodium, and an outer m mbrane f a wat r-insoluble coating material.

Additionally, the present invention is directed to the methods for preparing such Time-Controlled Explosion Systems.

When T.C.E.S. are placed into the gastro-intestinal tract, gastro fluid penetrates through the outer membrane into the T.C.E.S. and swells the swelling agent incorporated into the T.C.E.S. to result in the explosion of the outer membrane. That is, the release of the drug occurs by explosion of the outer membrane. When the form of T.C.E.S. is a tablet, the drug is released quickly after the explosion of the outer membrane, while when the form of T.C.E.S. is beads or granules, drug is released with zero order pattern after a definite lag time because of the time variance of the explosion of the outer membrane in each bead or granule.

From extensive studies, it is found that the explosion of the outer membrane is caused by the power of swelling occurred when swelling agent absorbs the fluid. This is the reason why T.C.E.S. are not influenced by the solubility or the dissolution rate of the drug and pH of the gastro-intestinal fluid and the drug is completely released from T.C.E.S.. In addition, it is possible to get the sustained release dosage forms with various release patterns by mixing T.C.E.S. which have different lag times. T.C.E.S. of the present invention have the following advantages; (i) the release rate or pattern is hardly influenced by the solubility or the dissolution rate of the drug, (ii) the release rate or pattern is independent of pH of the dissolution medium, and (iii) the drug is completely released. In addition, the sustained release dosage form with the various release patterns such as repeat, zero-order, reverse first-order pattern, sigmoid pattern and so on can be obtained by mixing the T.C.E.S. which have different lag times. In case that the form of T.C.E.S. is tablet, repeat pattern can be obtained by combining with non-sustained parts. The lag times can be controlled by the sort or amount of the swelling agent and membrane, and the size of T.C.E.S.. The suitable form of T.C.E.S. may be, for example, bead, granule or tablet. Both basic drugs and acidic drugs are applied to T.C.E.S. of the present invention.

Basic drugs are, for example, Metoclopramide, Sulpiride, Metoprolol tartrate, Tiapride, Zotepine and Cimetidine. Acidic drugs are, for example, Diclofenac, penicillin and cephalosporine antibiotics. Among these drugs, water-insoluble drug like FK235 substance may be converted, for example, into water-soluble solid dispersion composition. This solid dispersion composition is prepared by dispersing said drug into water-soluble polymer [e.g. hydroxypropylmethylcellulose, polyethylene glycol derivatives (e.g. polyethylene glycol 6000, polyethylene glycol 1500, ), ].

One type of T.C.E.S. of the present invention in which the form is beads or granules can be prepared as follows. Firstly, the drug-coated or drug-comprised beads and granules are prepared by conventional procedures. For example, nonpareil® (granule of sucrose; Trademark; prepared by Freund Co., Ltd.) seeds are placed and rolled in centrifugal granulator or blown up by air in fluid bed granulator. Drug is coated onto the seeds with a spraying binder (e.g. hydroxypropylmethylcellulose, methylcellulose, polyvinylpyrrolidone and sodium alginate,.) dissolved in a suitable solvent (e.g. water or ethanol,.). An alternative method which makes beads or granules comprising drug, diluents (e.g. sucrose, lactose, mannitol and microcrystalline cellulose) and additives used ordinally in this field by conventional procedures is also available.

Next, the swelling agent is coated on the drug-coated or drug-comprised beads and granules by the same procedure described above. The swelling agents used are disintegrating agent [e.g. low substituted hydroxypropylcellulose, Ac-Di-Sol® (carboxymethylcellulose sodium; Trademark; prepared by FMC Inc.) and Explotab® (sodium starch glycolate; Trademark; prepared by Edward Mendell Co., Ltd.) Low substituted hydroxypropylcellulose is defined as cellulose substituted with hydroxypropyl in which the ratio of hydroxypropoxyl group is 5 to 16 weight percent. The number of layers of the drug and the swelling agent are not limited to one respectively in the T.C.E.S.. That is, several drug layers and several swelling agent layers can be coated alternatively according to the same procedure as described above, if necessary, to get various release patterns. The ratio of the drug and the swelling agent in the beads or granules is preferably 0.1 to 50 and 30 to 80 weight percent respectively, but is not restricted to the above ratio, and can be changed in accordance with the dose or the lag times to be required respectively. Another type of T.C.E.S. of the present invention in which the form is beads or granules can be prepared firstly as follows.

Nonpareil® seeds are coated with a mixture of drug and swelling agent by the same procedure as described above. An alternative method which makes beads or granules comprising drug, swelling agent, diluents (e.g. sucrose, lactose, mannitol and microcrystalline cellulose) and additives used ordinarilly in this field by conventional procedures is also available.

The ratio of the drug and the swelling agent in the beads or granules is the same as one exemplifi d above. Another type of T.C.E.S. of the present invention in which the form is tablet can be prepared firstly according to conventional procedur , for example, by compressing the mixture of drug, swelling agent, diluents and lubricants (e.g. magnesium stearate,.). The ratio of the drug and the swelling agent in the tablet is preferably 0.1 to 30 and 10 to 60 weight percent respectively, but is not restricted to the above ratio.

Finally, swelling ag nt-coated or comprised beads, granules and tablets prepared by th methods described above are coated with the water-insoluble coating material with additives (e.g. talc, polyethylene glycol, silicone, diethylsebacate, and titanium dioxide) to form outer membrane by conventional procedur s. For example, the above-mentioned preparations are placed and blown up by air in fluid bed granulator, and then water-insoluble coating material dissolved in a suitable solvent (e.g. ethanol or dichloromethane,) and additives are coated on the above-mentioned preparations. The water-insoluble coating material used is, for example, ethylcellulose, hydroxypropylcellulose, shellac, polymethylstyrene, polyvinylacetate, polydiethylaminomethylstyrene, dimethylaminoethylmethacrylate-methylmethacrylate acid-co-polymer [e.g. Eudragit® E-30D, Eudragit® RL, Eudragit® RS (Trademarks; prepared by Röhm Pharma Co., Ltd.)] and wax. Among these water-insoluble coating materials, ethylcellulose is preferable because ethylcellulose membrane explodes easily when the swelling agent is swelled.

The ratio of the water-insoluble coating material for the above-mentioned preparations is preferably 1 to 50 weight percent, but is not restricted to the above ratio, and can be changed in accordance with the lag times to be required.

The size of T.C.E.S. of the present invention is preferably 0.5 mm to 20 mm in diameter.

To illustrate the effect of T.C.E.S. of the present invention, dissolution test data and absorption test data are shown in the following.

Dissolution Test 1

Test preparations (Drug : Metoclopramide)

| | |
|---|---|
| Sample A : | Preparation disclosed in Example 3 in which the concentration of ethylcellulose is 7.0 weight % |
| Sample B : | Preparation disclosed in Example 3 in which the concentration of ethylcellulose is 14.2 weight % |
| Sample C : | Preparation disclosed in Example 3 in which the concentration of ethylcellulose is 29.4 weight % |
| Sample D : | Preparation disclosed in Reference 1 in which the concentration of ethylcellulose is 5.0 weight % |
| Sample E : | Preparation in which Sample A and Sample C are mixed in the drug concentration ratio of three to one |
| Sample F : | Preparation in which Sample A and Sample C are mixed in the drug concentration ratio of one to one |
| Sample G : | Preparation in which Sample A and Sample C are mixed in the drug concentration ratio of one to three |
| Sample H : | Preparation disclosed in Example 9 |
| Sample I : | Preparation disclosed in Example 10 |

Test method

(I) The pharmacopoeia of Japan 10th edition Dissolution method II (Paddle method) Dissolution medium : First fluid (pH 1.2) 900ml, 37° C, l00r.p.m.

(II) The pharmacopoeia of Japan 10th edition Dissolution method II (Paddle method) Dissolution medium : Second fluid (pH 6.8) 900ml, 37° C, l00r.p.m.

Test result

Dissolution test data are shown in Tables l, 2, 3, 4 and 5.

Table 1

| Test Preparation | Test method | Dissolution rate (%) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 0.5hr | 1hr | 1.5hr | 2 hr | 3 hr | 4 hr | 5 hr | 6 hr | 7 hr | 8 hr |
| Sample A | I | 5 | 63 | 91 | 95 | 98 | 99 | 100 | 100 | 100 | 100 |
| | II | 4 | 54 | 90 | 95 | 98 | 99 | 100 | 100 | 100 | 100 |
| Sample B | I | 0 | 0 | 0 | 4 | 29 | 83 | 99 | 100 | 100 | 100 |
| | II | 0 | 0 | 0 | 3 | 26 | 81 | 99 | 100 | 100 | 100 |
| Sample C | I | 0 | 0 | 0 | 0 | 0 | 8 | 55 | 90 | 99 | 100 |
| | II | 0 | 0 | 0 | 0 | 0 | 6 | 54 | 85 | 96 | 100 |

Table 2

| Test Preparation | Test method | Dissolution rate (%) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 0.5hr | 1 hr | 1.5hr | 2 hr | 3 hr | 4 hr | 5 hr | 6 hr | 8 hr | 10 hr |
| Sample D | I | 21 | 38 | 49 | 56 | 64 | 68 | 72 | 74 | 78 | 83 |
| | II | 0 | 3 | 5 | 8 | 10 | 12 | 13 | 14 | 18 | 20 |

Table 3

| Test Preparation | Test method | Dissolution rate (%) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 0.5hr | 1 hr | 1.5hr | 2 hr | 3 hr | 4 hr | 5 hr | 6 hr | 7 hr | 8 hr |
| Sample E | II | 2 | 38 | 68 | 74 | 75 | 76 | 84 | 95 | 99 | 100 |
| Sample F | II | 2 | 30 | 46 | 48 | 49 | 51 | 69 | 87 | 96 | 99 |
| Sample G | II | 1 | 12 | 22 | 24 | 25 | 29 | 47 | 77 | 91 | 98 |

Table 4

| Test Preparation | Test method | Dissolution rate (%) | | | | |
|---|---|---|---|---|---|---|
| | | 1 hr | 2 hr | 4 hr | 6 hr | 8 hr |
| Sample H | I | 2 | 20 | 98 | 100 | 100 |
| | II | 0 | 14 | 91 | 99 | 100 |

Table 5

| Test Preparation | Test method | Dissolution rate (%) | | | |
|---|---|---|---|---|---|
| | | 1 hr | 1.25 hr | 1.5 hr | 2 hr |
| Sample I | II | 0 | 95 | 98 | 100 |

Dissolution Test 2

Test preparations (Drug Metoprolol tartrate)

Sample J : Preparation disclosed in Example 8
Sample K : Preparation disclosed in Reference 2 (control)

Test method

Test methods are the same as ones described in Dissolution Test I.

Test result

Dissolution test data are shown in Table 6.

Table 6

| Test Preparation | Test method | Dissolution rate (%) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 0.25 hr | 1 hr | 2 hr | 3 hr | 4 hr | 5 hr | 6 hr | 7 hr |
| Sample J | I | 0 | 1 | 2 | 39 | 67 | 92 | 95 | 100 |
| | II | 0 | 0 | 2 | 20 | 89 | 94 | 99 | 100 |
| Sample K | I | 100 | - | - | - | - | - | - | - |
| | II | 100 | - | - | - | - | - | - | - |

Absorption Test

Test method

Test preparations (Sample J and Sample K) were administered orally to three Beagle dogs weighing about 10 kg that were fasted overnight.

Dose of each test preparation was 120 mg as Metoprolol tartrate.

0.5, I, 2, 4, 6, 8 and 10 hours after oral administration, blood was collected into a heparinized tube.
After centrifuging, plasma concentrations of Metoprolol were measured by high pressure liquid chromatography.

Test result

Test result is shown in Tabl 7. Plasma concentration was shown by the m an-value from three dogs.

Table 7

| Test Preparation | plasma concentration (ng/ml) | | | | | | |
|---|---|---|---|---|---|---|---|
| | 0.5 hr | 1 hr | 2 hr | 4 hr | 6 hr | 8 hr | 10 hr |
| Sample J | N.D. | N.D. | 61 | 479 | 294 | 172 | 109 |
| Sample K (control) | 519 | 752 | 736 | 412 | 150 | 112 | 79 |
| ( N.D.: plasma concentration was not detected ) | | | | | | | |

Release patterns of the T.C.E.S. of the present invention in which the drug and the swelling agent are separated are shown in Table 1. These data show that the drug begins to release after a definite time and the drug is completely released with the zero-order pattern after the sample is subjected to the dissolution test.

As shown in Table 1, the lag times increase with the membrane thickness. In addition, the release rate and pattern is independent of pH, whereas, as shown in Table 2, the drug containing beads coated with the membrane in the absence of the swelling agent (Sample D) give the release rate which is dependent on pH of the dissolution medium and the drug is not completely released from this beads even after 10 hours, though the membrane is thinner than the above T.C.E.S. of the present invention (i.e. Samples A to C).

The representative release patterns of the drug from the mixture of Sample A and Sample C are shown in Table 3.

As apparent from Table 3, T.C.E.S. of the present invention provide for the new type of the oral sustained release preparations in which the release rate and pattern are freely controlled.

Release pattern of the another type of T.C.E.S. of the present invention in which drug and swelling agent are mixed is shown in Table 4.

Release pattern is almost the same as ones of T.C.E.S. as stated above in which the drug and the swelling agent are separated.

Release pattern of the T.C.E.S. in which the preparation form is tablet is shown in Table 5.

As shown in Table 5, drug is released quickly from this type of T.C.E.S. after a definite lag time.

Absorption test data are shown in Table 7.

These data show that plasma concentration of Metoprolol is not detected until 1 hour, slightly detected at 2 hour and is attained to maximum at 4 hour after oral administration of T.C.E.S. of the present invention (Sample J), whereas high plasma concentration is detected at 0.5 hour after oral administration of Sample K (control).

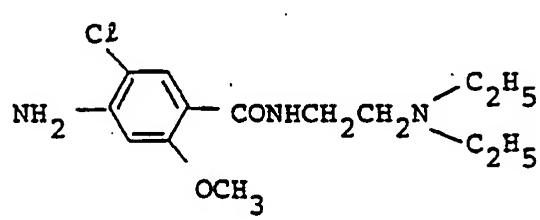
This absorption test data reflects the dissolution test data shown in Table 6; namely, Metoprolol is not released until 1 hour, slightly released at 2 hour and mostly released at 4 hour from T.C.E.S. of the present invention (Sample J).

These data suggest that sustained plasma concentration can be obtained by mixing T.C.E.S. which have different lag time, for example, shown in Table 1.

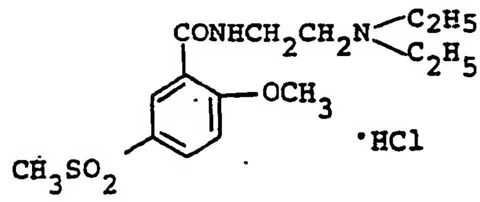
As mentioned above, the T.C.E.S. of the present invention have many excellent advantages and have solved many problems of the prior art.

The present invention is illustrated according to the examples as shown below. The chemical names and formulae of the drugs in the examples are shown below.

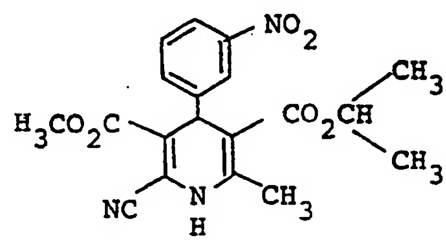
(i) Chemical name: 2-methoxy-4-amino-5-chloro-N($\beta$-diethylaminoethyl) benzamide (Metoclopramide)
Formula ;



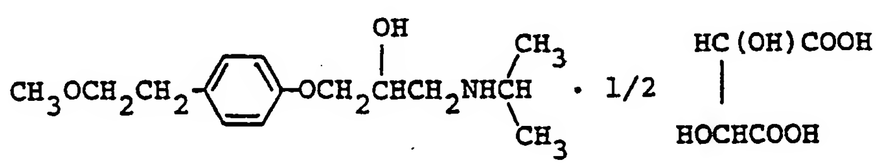
(ii) Chemical name: N-[2-(diethylamino)ethyl]-5-(methylsolfonyl)-o-anisamid hydrochloride (Tiapride)
Formula ;



(iii) Chemical name: 5-isopropyl 3-methyl 2-cyano-1,4-dihydro-6-methyl-4-(m-nitrophenyl)-3,5-pyridinedicarboxylate (FK235 substance)
Formula ;



(iv) Chemical name: dℓ-l-(isopropylamino)-3-[p-(2-methoxyethyl) phenoxy]-2-propanol hemi-L-tartrate (Metoprolol tartrate)
Formula ;



Example 1

Nonpareil® seeds (2 kg) were placed and rolled in a centrifugal granulator.
Metoclopramide (670 g) was coated on said Nonpareil® seeds with spraying hydroxypropylmethylcellulose (36 g) dissolved in water (720 g).

Example 2

The drug-coated beads (1.05 kg) prepared in Example 1 were placed and rolled in a centrifugal granulator.
Low substituted hydroxypropylcellulose (1.65 kg) was coated on said beads with spraying hydroxypropylmethylcellulose (0.209 kg) dissolved in ethanol-water mixture (85:15 V/V %) (4.18 ℓ).

Example 3

The swelling agent-coated beads (100 g) prepared in Example 2 were placed and blown up with air in a fluid bed granulator.
Ethylcellulose dissolved in ethanol and talc was sprayed to coat on said beads to give the d sired preparations. Three preparations wherein the concentration of ethylcellulose is 7.0, 14.2 and 29.4 weight % for the beads pr pared in Example 2 were prepared.

Example 4

Time-Controlled Explosion System, wherein core is Nonpareil seed (420 g), drug is Metoclopramide (140 g), swelling agent is Explotab® (840 g) and water-insoluble coating material contains ethylcellulose and talc, was prepared according to similar procedures to those of Examples 1, 2 and 3.
The concentration of ethylcellulose for the beads prepared according to a similar procedure to that of Example 2 is 17.7 weight %.

Example 5

Time-Controlled Explosion System, wherein core is Nonpareil seed (420 g), drug is Metoclopramide (140 g), swelling agent is Ac-Di-Sol® (840 g) and water-insoluble coating material contains ethylcellulose and talc, was prepared according to similar procedures to those of Examples 1, 2 and 3.
The concentration of ethylcellulose for the beads prepared according to a similar procedure to that of Example 2 is 21.8 weight %.

Example 6

Time-Controlled Explosion System, wherein core is Nonpareil® seed (778 g), drug is Tiapride (158 g), swelling agent is low substituted hydroxypropylcellulose (870 g) and water-insoluble coating material contains ethylcellulose and talc, was prepared according to similar procedures to those of Examples 1, 2 and 3.
The concentration of ethylcellulose for the beads prepared according to a similar procedure to that of Example 2 is 21.2 weight %.

Example 7

FK235 substance (2 g) was dissolved in a mixture of polyethylene glycol 1500 and polyethylene glycol 6000 (1:1 W/W) (100 g) with heating. After cooling, granules which contain FK235 substance were prepared according to the conventional method.
Thereafter, Time-Controlled Explosion System, wherein swelling agent is low substituted hydroxypropylcellulose (500 g) and water-insoluble coating material contains ethylcellulose and talc, was prepared according to similar procedures to those of Examples 2 and 3.
The concentration of ethylcellulose for the granules prepared according to a similar procedure to that of Example 2 is 10.5 weight %.

Example 8

Time-Controlled Explosion System, wherein core is Nonpareil® seed (392 g), drug is Metoprolol tartrate (168 g), swelling agent is low substituted hydroxypropylcellulose (840 g) and water-insoluble coating material contains ethylcellulose and talc, was prepared according to similar procedures to those of Examples 1, 2 and 3.
The concentration of ethylcellulose for the beads prepared according to a similar procedure to that of Example 2 is 12.65 weight %.

Example 9

Nonpareil® seeds (500 g) were placed and rolled in a centrifugal granulator.
Metoclopramide (170 g) and low substituted hydroxypropylcellulose (1000 g) were mixed and the mixture was coated on said nonpareil® seeds with spraying hydroxypropylmethylcellulose (150 g) dissolved in ethanol-water mixture (85:15 V/V %) (3ℓ).
Ethylcellulose dissolved in ethanol and talc was sprayed to coat on the seeds as obtained to give Time-Controlled Explosion System.
The concentration of ethylcellulose for the beads as obtained is 13.2 weight %.

Example 10

Metoclopramide (7.7 g), lactose (42 g), microcrystalline cellose (30 g), Ac-Di-Sol® (20 g) and magne-

sium stearate (0.3 g) were mixed and the mixture was compressed into tablets. Ethylcellulose dissolved in ethanol was sprayed to coat on said tablets to give Time-Controlled Explosion Syst m.
One tablet has the following formula :

| | |
|---|---|
| Metoclopramide | 7.7 mg |
| lactose | 42 mg |
| microcrystalline cellulose | 30 mg |
| Ac-Di-Sol® | 20 mg |
| magnesium stearate | 0.3 mg |
| ethylcellulose | 5.2 mg |
| | 105.2 mg |

Reference 1

For the purpose of comparing with the preparation prepared in Example 3, Metoclopramide beads (105 g) coated with ethylcellulose without swelling agent were prepared according to similar procedures to those of Examples 1 and 3 without the process described in Example 2.
The concentration of ethylcellulose for the Metoclopramide beads is 5.0 weight %.

Reference 2

For the purpose of comparing with the preparation prepared in Example 8, Metoprolol tartrate beads (560 g) without swelling agent and water-insoluble coating material were prepared according to a similar procedure to that of Example 1.

Brief description of the drawings are as follows. Fig. 1 shows a sectional structure of T.C.E.S. disclosed in Examples 3 to 6 and 8 in which (1) is a seed of sucrose (core), (2) is a drug, (3) is a swelling agent and (4) is membrane respectively.
Fig. 2 shows a sectional structure of T.C.E.S. disclosed in Example 7 in which (2a) is a core comprising drug (3) is a swelling agent and (4) is membrane respectively. Fig. 3 shows a sectional structure of T.C.E.S. disclosed in Example 9 in which (1) is a seed of sucrose (core), (2b) is a mixture comprising drug and swelling agent and (4) is membrane respectively.
Fig. 4 shows a sectional structure of T.C.E.S. disclosed in Example 10 in which (2b) is a mixture comprising drug and swelling agent and (4) is membrane respectively.

**Claims**

1. A Time-Controlled Explosion System in which drug release is caused by explosion of outer membrane of a water-insoluble coating material after a definite time period, said System comprising a preparation in the form of a bead or granule, said preparation comprising a core which is covered with an outer layer of drug, a further layer of disintegrating agent selected from cellulose substituted with hydroxypropyl in which the ratio of hydroxypropoxyl group is 5 to 16 weight percent, sodium starch glycolate and carboxymethylcellulose sodium, and an outer membrane of a water-insoluble coating material.

2. A Time-Controlled Explosion System in which drug release is caused by explosion of outer membrane of a water-insoluble coating material after a definite time period, said System comprising a preparation in the form of a bead or granule, said preparation comprising a core of a drug which is covered with an outer layer of disintegrating agent selected from cellulose substituted with hydroxypropyl, in which the ratio of hydroxypropoxyl group is 5 to 16 weight percent , sodium starch glycolate and carboxymethylcellulose sodium, and an outer membrane of a water-insoluble coating material.

3. A Time-Controlled Explosion System in which drug release is caused by explosion of out r membrane of a water-insoluble coating material after a definite time period, said System comprising a preparation in the form of a bead or granule, said preparation comprising a core which is cov r d with an out r layer of a mixtur of a drug and a disintegrating agent selected from cellulos substitut d with hydroxypropyl in which th ratio of hydroxypropoxyl group is 5 to 16 weight p rcent , sodium starch glycolate and carboxymethylcellulose sodium, and an outer membrane of a water-insoluble coating

material.

4. A Time-Controlled Explosion System according to claims 1 to 3 wherein the water-insoluble coating material comprises ethylcellulose.

5. A Time-Controlled Explosion System according to claims 1 to 3, characterized in mixing preparations which have different lag times to obtain sustained release preparations with various release patterns.

6. A method for preparing a Time-Controlled Explosion System in which drug release is caused by explosion of outer membrane of a water-insoluble coating material after a definite time period, characterised in that after preparing a core such core is covered with an outer layer of drug, a further layer of disintegrating agent selected from cellulose substituted with hydroxypropyl in which the ratio of hydroxypropoxyl group is 5 to 16 weight percent, sodium starch glycolate and carboxymethylcellulose sodium is coated thereon, and then water-insoluble coating material is further coated thereon.

7. A method for preparing a Time-Controlled Explosion System in which drug release is caused by the explosion of an outer membrane of a water-insoluble coating material after a definite time period characterized in that after preparing beads or granules comprising a drug, disintegrating agent selected from cellulose substituted with hydroxypropyl in which the ratio of hydroxypropoxyl group is 5 to 16 weight percent , sodium starch glycolate and carboxymethylcellulose sodium is firstly coated thereon and then a water-insoluble coating material is further coated thereon.

8. A method for preparing a Time-Controlled Explosion System in which drug release is caused by the explosion of an outer membrane of a water-insoluble coating material after a definite time period characterized in that after preparing a core, a mixture comprising a drug and a disintegrating agent selected from cellulose substituted with hydroxypropyl in which the ratio of hydroxypropoxyl group is 5 to 16 weight percent , sodium starch glycolate and carboxymethylcellulose sodium is coated thereon and then a water-insoluble coating material is coated thereon.

## Revendications

1. Système d'explosion à retardement dans lequel la libération d'un médicament est provoquée par l'explosion d'une membrane externe d'une matière de revêtement insoluble dans l'eau au bout d'un temps déterminé, ce système comprenant une préparation sous la forme d'une perle ou d'un granulé, cette préparation comportant un noyau qui est recouvert d'une couche externe de médicament, d'une autre couche d'agent désintégrant choisi parmi la cellulose substituée par des groupes hydroxypropyle, dans laquelle le rapport des groupes hydroxypropoxyle est de 5 à 16 % en poids, le glycolate d'amidon sodique et la carboxyméthylcellulose sodique, et d'une membrane externe d'une manière de revêtement insoluble dans l'eau.

2. Système d'explosion à retardement, dans lequel la libération d'un médicament est provoquée par l'explosion d'une membrane externe d'une matière de revêtement insoluble dans l'eau au bout d'un temps déterminé, ce système comprenant une préparation sous la forme d'une perle ou d'un granulé, cette préparation comprenant un noyau d'un médicament qui est recouvert d'une couche externe d'un agent désintégrant choisi parmi la cellulose substituée par des groupes hydroxypropyle, dans laquelle le rapport des groupes hydroxypropoxyle est de 5 à 16 % en poids, le glycolate d'amidon sodique et la carboxyméthylcellulose sodique, et d'une membrane externe d'une matière de revêtement insoluble dans l'eau.

3. Système d'explosion à retardement dans lequel la libération d'un médicament est provoquée par l'explosion d'une membrane externe d'une matière de revêtement insoluble dans l'eau au bout d'un temps déterminé, ce système comprenant une préparation sous la forme d'une perle ou d'un granulé, cette préparation comprenant un noyau qui est recouvert d'une couche ext rne d'un mélang d'un médicament t d'un agent désintégrant choisi parmi la cellulose substitué par des groupes hydroxypropyl , dans laquell le rapport d s group s hydroxypropoxyl st de 5 à 16 %, le glycolate d'amidon sodique t la carboxyméthylcellulose sodique et d'une membrane externe d'une matièr d r v^t ment insolubl dans l' au.

4. Système d'explosion à retardement selon les revendications 1 à 3, dans lequ l la matière de revêtement insoluble dans l'eau comprend de l éthylcellulose.

5. Système d'explosion à retardement selon les revendications 1 à 3, caractérisé en ce qu'on mélange des préparations qui ont des temps de retard différents pour obtenir des préparations à libération prolongée ayant divers profils de libération.

6. Procédé pour préparer un système d'explosion à retardement dans lequel la libération d'un médicament est provoquée par l'explosion d'une membrane externe d'une matière de revêtement au bout d'un temps déterminé, caractérisé en ce qu'après avoir préparé un noyau, on recouvre ce noyau d'une couche externe d'un médicament, on applique sur celle-ci une nouvelle couche d'agent désintégrant choisi parmi une cellulose substituée par des groupes hydroxypropyle dans laquelle le rapport des groupes hydroxypropoxyle est de 5 à 16 % en poids, un glycolate d'amidon sodique et une carboxyméthylcellulose sodique, puis on applique encore sur celle-ci une matière de revêtement insoluble dans l'eau.

7. Procédé de préparation d'un système d'explosion à retardement dans lequel la libération d'un médicament est provoquée par l'explosion d'une membrane externe d'une membrane de revêtement insoluble dans l'eau au bout d'un temps déterminé, caractérisé en ce qu'après avoir préparé des perles ou granulés comprenant un médicament, on applique d'abord sur ceux-ci un agent désintégrant choisi parmi une cellulose substituée par des groupes hydroxypropyle dans laquelle le rapport des groupes hydroxypropoxyle est de 5 à 16 % en poids, le glycolate d'amidon sodique et la carboxyméthylcellulose sodique, puis on applique encore sur ceux-ci une matière de revêtement insoluble dans l'eau.

8. Procédé de préparation d'un système d'explosion à retardement, dans lequel la libération d'un médicament est provoquée par l'explosion d'une membrane externe d'une matière de revêtement insoluble dans l'eau au bout d'un temps déterminé, caractérisé en ce qu'après avoir préparé un noyau, on applique sur celui-ci un mélange comprenant un médicament et un agent désintégrant choisi parmi une cellulose substituée par des groupes hydroxypropyle dans laquelle le rapport des groupes hydroxypropoxyle est de 5 à 16 % en poids, le glycolate d'amidon sodique et la carboxyméthylcellulose sodique, puis on applique sur celui-ci une matière de revêtement insoluble dans l'eau.

## Patentansprüche

1. Zeitgesteuertes Explosionssystem, in dem die Freisetzung eines Arzneimittels bewirkt wird durch die Explosion einer äußeren Membran aus einem wasserunlöslichen Beschichtungsmaterial nach einer definierten Zeitspanne, wobei das System umfaßt ein Präparat in Form einer Perle oder eines Körnchens, wobei das Präparat umfaßt einen Kern, der mit einer äußeren Schicht aus einem Arzneimittel überzogen ist, einer weiteren Schicht aus einem Desintegrationsmittel, ausgewählt aus Cellulose, die durch Hydroxypropyl substituiert ist, in der der Anteil an Hydroxypropoxygruppen 5 bis 16 Gew.-% beträgt, Natriumstärkeglycolat und Carboxymethylcellulosenatrium, sowie eine äußere Membran aus einem wasserunlöslichen Beschichtungsmaterial.

2. Zeitgesteuertes Explosionssystem, in dem die Freisetzung eines Arzneimittels bewirkt wird durch Explosion einer äußeren Membran aus einem wasserunlöslichen Beschichtungsmaterial nach einer definierten Zeitspanne, wobei das System umfaßt ein Präparat in Form einer Perle oder eines Körnchens, wobei das Präparat umfaßt einen Kern aus einem Arzneimittel, der überzogen ist mit einer äußeren Schicht aus einem Desintegrationsmittel, ausgewählt aus Cellulose, die durch Hydroxypropyl substituiert ist, in der der Anteil an Hydroxypropoxygruppen 5 bis 16 Gew.-% beträgt, Natriumstärkeglycolat und Carboxymethylcellulosenatrium, und eine äußere Membran aus einem wasserunlöslichen Beschichtungsmaterial.

3. Zeitgesteu rtes Explosionssystem, in dem die Freisetzung eines Arzneimittels durch Explosion einer äußeren Membran aus einem wasserunlöslichen Beschichtungsmaterial nach einer definierten Zeitspanne bewirkt wird, wobei das System umfaßt ein Präparat in Form einer Perle oder eines Kömchens, wob i das Präparat umfaßt einen K rn, der üb rzogen ist mit einer äußeren Schicht aus einem Gemisch aus einem Arzneimittel und einem Desintegrationsmittel, ausgewählt aus Cellulose, die durch Hydroxypropyl substituiert ist, wobe i der Mengenanteil an Hydroxypropoxygruppen 5 bis 16 Gew.-%

beträgt, Natriumstärkeglycolat und Carboxymethylcellulosenatrium, und in äußer Membran aus einem wasserunlöslichen Beschichtungsmaterial.

4. Zeitgesteuertes Explosionssystem nach den Ansprüchen 1 bis 3, worin das wasserunlösliche Beschichtungsmaterial Ethylcellulose umfaßt.

5. Zeitgesteuertes Explosionssystem nach den Ansprüchen 1 bis 3, dadurch gekennzeichnet, daß Präparate gemischt werden, die unterschiedliche Verzögerungszeiten aufweisen, zur Herstellung von Präparaten mit kontinuierlicher Freisetzung, die verschiedene Freisetzungsmuster aufweisen.

6. Verfahren zur Herstellung eines zeitgesteuerten Explosionssystems, in dem die Freisetzung eines Arzneimittels durch Explosion einer äußeren Membran aus einem wasserunlöslichen Beschichtungsmaterial nach einer definierten Zeitspanne bewirkt wird, dadurch gekennzeichnet, daß nach der Herstellung eines Kerns dieser Kern mit einer äußeren Schicht aus einem Arzneimittel überzogen wird, eine weitere Schicht aus einem Desintegrationsmittel, ausgewählt aus Cellulose die durch Hydroxypropyl substituiert ist, in der der Mengenanteil an Hydroxypropoxygruppen 5 bis 16 Gew.-% beträgt, Natriumstärkeglycolat und Carboxymethylcellulosenatrium, in Form einer Schicht darauf aufgebracht wird und dann eine weitere Schicht aus einem wasserunlöslichen Beschichtungsmaterial aufgebracht wird.

7. Verfahren zur Herstellung eines zeitgesteuerten Explosionssystems, in dem die Freisetzung eines Arzneimittels durch die Explosion einer äußeren Membran aus einem wasserunlöslichen Beschichtungsmaterial nach einer definierten Zeitspanne bewirkt wird, dadurch gekennzeichnet, daß nach der Herstellung von Perlen oder Körnchen, die ein Arzneimittel enthalten, ein Desintegrationsmittel, ausgewählt aus Cellulose, die durch Hydroxypropyl substituiert ist, in der der Mengenanteil an Hydroxypropoxygruppen 5 bis 16 Gew.-% beträgt, Natriumstärkeglycolat und Carboxymethylcellulosenatrium, zuerst in Form einer Schicht darauf aufgebracht wird und dann eine weitere Schicht aus einem wasserunlöslichen Beschichtungsmaterial aufgebracht wird.

8. Verfahren zur Herstellung eines zeitgesteuerten Explosionssystems, in dem die Freisetzung eines Arzneimittels durch die Explosion einer äußeren Membran aus einemwasserunlöslichen Beschichtungsmaterials nach einer definierten Zeitspanne bewirkt wird, dadurch gekennzeichnet, daß nach der Herstellung eines Kerns ein Gemisch, das umfaßt ein Arzneimittel und ein Desintegrationsmittel, ausgewählt aus Cellulose, die durch Hydroxypropyl substituiert ist, in der der Mengenanteil an Hydroxypropoxygruppen 5 bis 16 Gew.-% beträgt, Natriumstärkeglycolat und Carboxymethylcellulosenatrium, in Form einer Schicht darauf aufgebracht wird und dann ein Überzug aus einem wasserunlöslichen Beschichtungsmaterial aufgebracht wird.

Fig.1

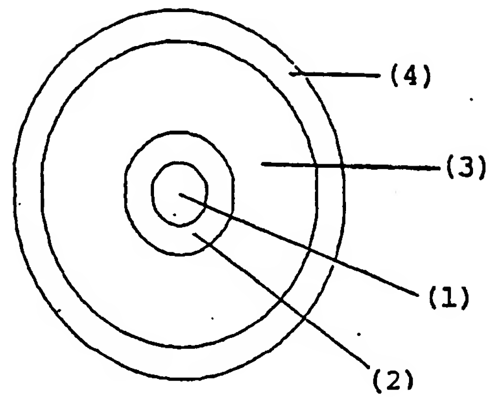



Fig.2

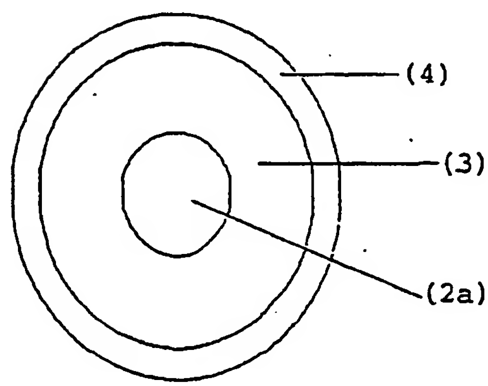



Fig.3

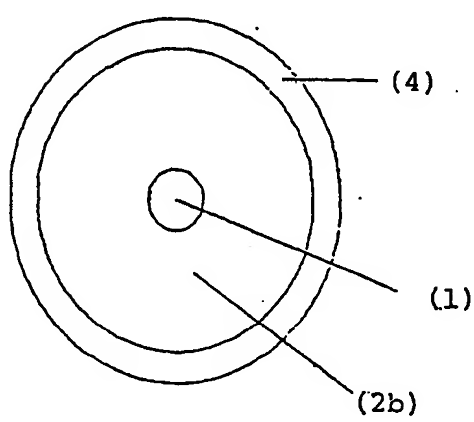



Fig.4